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(57) Abstract

Novel formulations are disclosed for the administration of an avermectin, based upon the use of N-methylpyrrolidone or 2-pyrrolidone or mixtures thereof to dissolve avermectin. Formulations can contain from 0.1 % to 40 % by weight dissolved in at least 5 % by volume of N-methylpyrrolidone, 2-pyrrolidone or mixture thereof. Various formulations are suitable for administration by intramuscular or subcutaneous injection, by topical application, stomach intubation, oral and drench administration.

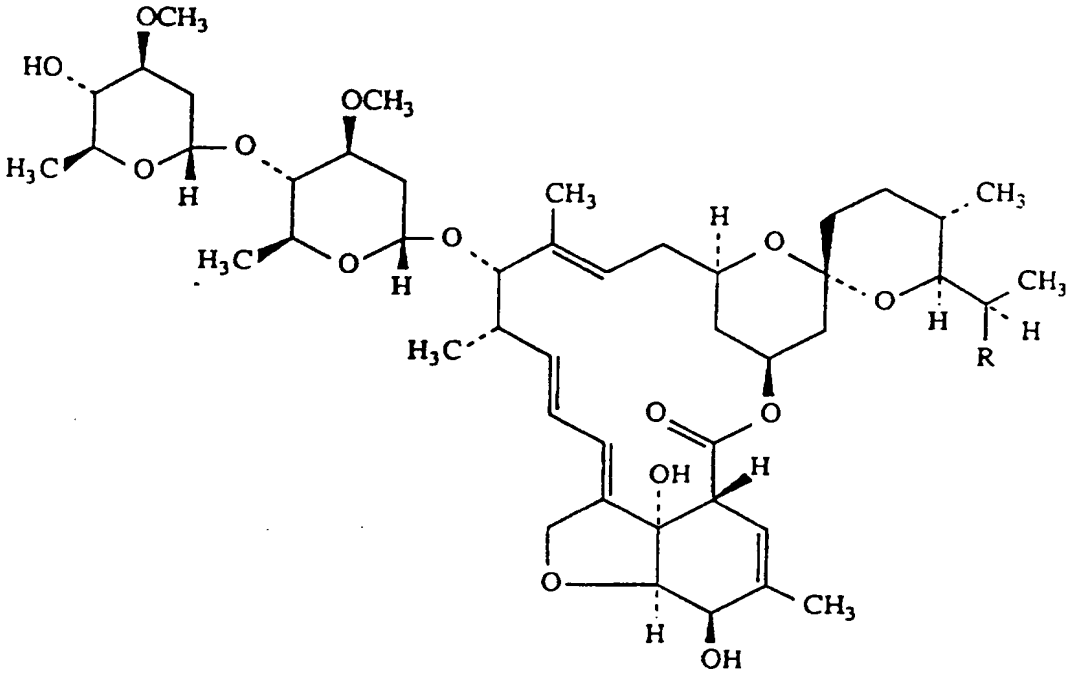
AVERMECTIN FORMULATION

FIELD OF THE INVENTION

The invention relates to novel formulations for the administration of therapeutic doses of avermectins generally and ivermectin in particular.

BACKGROUND OF THE INVENTION

The avermectins are a family of closely related compounds produced by *Streptomyces avermitilis* or by synthetic or semi-synthetic means. A representative structure is shown for ivermectin which is semi-synthetic derivative: 22,23-dihydro-avermectin B_1, containing at least 80% 22,23-dihydroavermectin B_{1a} and not more than 20% 22,23-dihydroavermectin B_{1b}:



component B_{1a}, $R = C_2H_5$ component B_{1b}, $R = CH_3$

Members of the avermectin (C-076) family include other derivatives of pentacyclic 16-membered lactones, primarily A_{1a}, A_{2a}, B_{1a}, B_{2a} as well as minor components A_{1b}, A_{2b}, B_{1b}, B_{2b}, all of which share to some degree activity as antiparasitics and antiagaricidics. Ivermectin has been marketed for treatment of various helminth intestinal parasites and heartworm in animals and for onchocerciasis (river blindness) in humans. The broad spectrum of activity of the avermectins make them attractive candidates for treatment of a variety of endo- and ectoparasites.

Ivermectin is described in U.S. patent 4,199,569. In common with other avermectins, ivermectin is poorly soluble in water, about 0.005 mg per ml at room temperature. Solubility in organic solvents varies, depending upon solvent, without clear trends. As reported by Fink, D.W. in Analytical Profiles of Drug Substances, Vol. 17:156-184, Academic Press, New York (1988), solubility in 1-butanol is 330 mg/ml but in 2-propanol is only 70 mg/ml. For ketone solvents, solubility in methylethylketone is 320 mg/ml but in acetone is only 81 mg/ml. Avermectin solubility in N-methylpyrrolidone has not been reported.

Two types of formulations for parenteral administration of ivermectin have been described. An aqueous micelle formulation is described in U.S. Patent 4,389,397. A soluble formulation is disclosed in U.S. Patent 4,853,372. The latter uses a solvent mixture of glycerol formal and propylene glycol (from 10:90 to 90:10) or of propylene glycol and water (from 95:5 to 80:20). The soluble formulations were said to be more effective against ectoparasites, such as ticks. Concentrations of from 0.1% to 20% by weight of ivermectin in the formulations were reported.

The use of N-methylpyrrolidone as a solvent for parenteral administration of oxytetracycline was disclosed in U.S. Patent 4,772,460 and in International Publication WO 94/27611. N-methylpyrrolidone was found to be more suitable as an injectable solvent than 2-pyrrolidone.

SUMMARY OF THE INVENTION

It has been unexpectedly found that avermectins are sufficiently soluble in N-methylpyrrolidone or 2-pyrrolidone and mixtures of the two, to permit them to be used as suitable solvents for ivermectin formulations for intramuscular injection, subcutaneous injection, topical pour-on, stomach intubation, oral and drench administration. Formulations of avermectins are disclosed herein, including N-methylpyrrolidone as solvent, together with stabilizers, extenders, surfactants, preservatives and the like for various treatment and dosage regimens, as understood in the art. Various formulations described herein using ivermectin can be made using any of the avermectins since the latter differ only slightly from one another in chemical structure.

Formulations of the invention including N-methylpyrrolidone, or 2-pyrrolidone and mixtures thereof, have the advantages of providing higher concentrations of avermectin, allowing smaller dose quantities to be delivered, having improved stability and extended shelf life, increased concentrations of avermectin in the bloodstream and other extracellular fluid compartments and less pain, swelling and tissue damage at the injection site compared to currently available formulations. N-methylpyrrolidone and 2-pyrrolidone can also be used for transdermal absorption applications such as pour-on formulations and transdermal patches. Formulations of the invention including N-methylpyrrolidone and/or 2-pyrrolidone can be designed to provide therapeutic levels of avermectin over a sufficient period of time to be more effective against ectoparasites.

DETAILED DESCRIPTION OF THE INVENTION

As noted, ivermectin has unexpectedly been found to be sufficiently soluble in N-methylpyrrolidone as well as 2-pyrrolidone to permit formulation of various therapeutic compositions. Both N-methylpyrrolidone and 2-pyrrolidone have been approved as a safe solvent for injection, but only for oxytetracycline; which is chemically unlike ivermectin. N-methylpyrrolidone is preferred for injection formulations since

it causes less pain at the injection site and less tissue reaction than does 2-pyrrolidone. Ivermectin can be present in the formulation from 0.1% to 40% (w/v). N-methylpyrrolidone (also known as M-pyrole) can be present from 5% to essentially 100% (v/v) of the formulation. The specific gravity of N-methylpyrrolidone is 1.027 at 25°C relative to water at 4°C. Additional compounds can be included as desired, e.g. propylene glycol up to 95% by volume, water up to 90% by volume and Clorsulon (an antiparasitic agent frequently co-administered with ivermectin) up to 40% by weight. The formulation can contain water up to amounts which limit avermectin solubility. The maximum amount of water which can be included depends upon the amount of avermectin and the presence of co-solvents such as propylene glycol, and presence of detergent, as illustrated in the Examples. The amount of water which can be present is limited only by avermectin solubility. The presence of too much water can be readily detected because the clear solution becomes milky or cloudy as excess water is added. Where N-methylpyrrolidone is the sole solvent, up to 30% by volume of water can be included in a formulation containing 1% (w/v) ivermectin. If less ivermectin is present, the amount of water can be increased somewhat. If 10% (v/v) propylene glycol is a co-solvent with 20% (w/v) N-methylpyrrolidone, 0.5% ivermectin remains soluble in the presence of water up to about 70% by volume. Compositions containing 2-pyrrolidone completely or partially substituted for N-methylpyrrolidone in the exemplified formulations are equivalent in their solubility properties. As noted above, compositions containing N-methylpyrrolidone are preferred.

The formulations are readily prepared by dissolving ivermectin (a white crystalline powder) or other avermectin compound or mixture thereof, in N-methylpyrrolidone and/or 2-pyrrolidone, then adding remaining components of the desired formulation to achieve the final desired concentration of the drug and final ratios of other compounds. Where a co-solvent is used, such as propylene glycol, the avermectin can be dissolved

in as much co[redacted]vent or N-methylpyrrolidon[redacted]o-solvent mixture as needed to dissolve the drug.

Sterilization of the formulation can be carried out by membrane filtration, provided the membrane filter material is itself insoluble in and compatible with the formulation.

A phenomenon encountered with parenteral administration of a water-insoluble drug is that the drug can precipitate at the injection site (subcutaneous or intramuscular) from which it becomes released slowly over a period of time. The phenomenon can be turned to advantage provided the amount deposited and rate of release combine to provide therapeutically effective drug levels without excessive swelling at the site of injection or tissue damage. For ivermectin formulations, control of ectoparasites requires therapeutic drug levels over a longer treatment period than for control of endoparasites. Certain formulations of the invention are advantageous for ectoparasite control in that they allow injection of a higher drug concentration than previous formulations, permitting deposition of therapeutically effective amounts of the drug in a smaller injection volume than heretofore. In addition, the formulations of the invention are compatible with *in situ* solubilizing agents such as polyvinylpyrrolidone or polyethylene glycol and with surfactants such as polysorbate 80. Such components provide more rapid absorption of the drug after intramuscular or subcutaneous injection. The use of such components improves safety for intramuscular injection. Since the N-methylpyrrolidone solvent is essentially an inert, aprotic solvent, the formulations are highly stable and the opportunity for activity loss due to reaction of avermectin with the solvent is minimized. The N-methylpyrrolidone-propylene glycol vehicle is further advantageous in being compatible with most antimicrobial preservatives such as benzyl alcohol and methyl-, ethyl- and propylparaben. A desired goal in the veterinary field is to provide a multiple-dose injection product that retains sterility with multiple uses. The ability to combine the avermectin with an antimicrobial preservative of low aqueous solubility, such as methylparaben, can provide sustained antimicrobial activity not

only within t[redacted]dispenser but also within [redacted] injection site. As a further advantage, N-methylpyrrolidone is able to promote transdermal absorption of avermectins. Formulations are therefore provided for topical transdermal patch and pour-on applications for both ecto- and endoparasite control. Formulations of the invention are also suitable for stomach intubation, oral and drench administration. N-methylpyrrolidone is known to have a very low order of oral toxicity (Rat LD_{50} 4200 mg/kg). Most of the compound is eliminated by the kidneys within 24 hours.

The following formulations are provided by way of exemplary embodiments of the invention. 2-Pyrrolidone can be substituted for all or part of the N-methylpyrrolidone in the following formulations:

GENERAL FORMULATIONS

Example 1 (Ivermectin Injection):

Ivermectin	0.10% w/v to 40% w/v
N-methylpyrrolidone	5% v/v to 100% v/v
Propylene Glycol	90% v/v to 0% v/v
Water	30% v/v to 0% v/v

Example 2 (Ivermectin-F Injection):

Ivermectin	0.10% w/v to 40% w/v
Clorsulon	0.10% w/v to 40% w/v
N-methylpyrrolidone	5% v/v to 100% v/v
Propylene Glycol	90% v/v to 0% v/v
Water	30% v/v to 0% v/v

Example 3:

Ivermectin	1% w/v (10 mg/mL)
N-methylpyrrolidone	100% v/v

Example 4:

Ivermectin	1% w/v (10 mg/mL)
N-methylpyrrolidone	70% v/v
Water	q.s. 30% v/v

Example 5:

Ivermectin	1% w/v (10 mg/mL)
Clorsulon	10% w/v (100 mg/mL)
N-methylpyrrolidone	30% v/v
Propylene Glycol	q.s. 70% v/v

Example 6:

Ivermectin	1% w/v (10 mg/mL)
Clorsulon	10% w/v (100 mg/mL)
N-methylpyrrolidone	q.s. approx. 100% v/v

Example 7 (Subcutaneous Injection):

Ivermectin	10 mg/mL
N-methylpyrrolidone	30% v/v
Propylene Glycol	q.s

Example 8 (Subcutaneous Injection):

Ivermectin	10 mg/mL
Clorsulon	100 mg/mL
N-methylpyrrolidone	30% v/v
Propylene Glycol	q.s.

Example 9 (Subcutaneous Injection):

Ivermectin	0.27% w/v
N-methylpyrrolidone	40% v/v
Water for Injection	10% v/v
Propylene Glycol	q.s.

Example 10 (Subcutaneous Injection):

Ivermectin	10 mg/mL
N-methylpyrrolidone	30% v/v
Benzyl Alcohol	1.5% v/v
Water for Injection	10% v/v
Propylene Glycol	q.s.

Example 11 (Intramuscular Injection):

Ivermectin	10 mg/mL
N-methylpyrrolidone	30% v/v
Polyvinylpyrrolidone	20% w/v
Methylparaben	0.18% w/v
Propylparaben	0.02% w/v
Propylene Glycol	q.s.

Example 12 (Intramuscular Injection):

Ivermectin	20 mg/mL
N-methylpyrrolidone	40% v/v
Polyethylene Glycol	30% w/v
Propylene Glycol	q.s.

Example 13 (Intramuscular Injection):

Ivermectin	10 mg/mL
N-methylpyrrolidone	30% v/v
Polyvinylpyrrolidone	20% w/v
Benzyl Alcohol	1.5% v/v
Propylene Glycol	q.s.

Example 14 (Intramuscular Injection):

Ivermectin	10 mg/mL
N-methylpyrrolidone	30% v/v
Polysorbate 80	10% v/v
Polyoxyethylene fatty acid ester	10% v/v
Benzyl Alcohol	1.5% v/v
Propylene Glycol	q.s.

Example 15 (Pour-on Formulation):

Ivermectin	5 mg/mL
N-methylpyrrolidone	20% v/v
Propylene Glycol	10% v/v
FD&C Blue #1	0.01 mg/mL
Purified Water	q.s.

Example 16 (Pour-on Formulation):

Ivermectin	5 mg/mL
N-methylpyrrolidone	10% v/v
Polysorbate 80	5% v/v
FD&C Blue #1	0.01 mg/mL
Benzyl Alcohol	1.5% v/v
Purified Water	q.s.

Example 17 (Stomach Intubation, Oral and Drench Formulation):

Ivermectin	10 mg/mL
N-methylpyrrolidone	5% v/v
Propylene Glycol	20% v/v
Polysorbate 80	10% v/v
Benzyl Alcohol	1.5% v/v
Purified Water	q.s.

Example 18 (S[redacted]ach Intubation, Oral and D[redacted]ch Formulation):

Ivermectin	10 mg/mL
N-methylpyrrolidone	20% v/v
Propylene Glycol	20% v/v
Benzyl Alcohol	1.5% v/v
Purified Water	q.s.

I claim:

1. Formulation for administering an avermectin consisting of from 0.1% to 40% by weight of an avermectin dissolved in a solvent comprising at least 5% by volume N-methylpyrrolidone, or 2-pyrrolidone, or a mixture thereof.
2. The formulation of claim 1 wherein the avermectin is ivermectin.
3. The formulation of claim 2 wherein the solvent is a mixture of N-methylpyrrolidone, or 2-pyrrolidone, or a mixture thereof, and propylene glycol.
4. The formulation of claim 3 further comprising up to 20% by weight polyvinylpyrrolidone.
5. The formulation of claim 2 comprising at least 10% N-methylpyrrolidone, or 2-pyrrolidone, or a mixture thereof, and further comprising up to 30% by volume water.
6. The formulation of claim 3 comprising at least 10% by volume propylene glycol, and further comprising water.
7. The formulation of claim 2 further comprising a surfactant.
8. The formulation of claim 2 further comprising a preservative.
9. The formulation of claim 2 further comprising Clorsulon.
10. The formulation of claim 2 further comprising polyethylene glycol up to 30% by weight.
11. A formulation according to claim 1 further comprising a maximum of 90% by volume propylene glycol.
12. A formulation according to claim 11 further comprising from 0.10% to 40% by weight Clorsulon.
13. A formulation according to claim 2 consisting essentially of 1% by weight ivermectin dissolved in N-methylpyrrolidone.
14. A formulation according to claim 2 consisting essentially of 1% by weight ivermectin, 70% by volume N-methylpyrrolidone, and water.
15. A formulation according to claim 6 comprising 1% by weight ivermectin, 10% by weight Clorsulon, and N-methylpyrrolidone.

16. A formulation according to claim 3 wherein the N-methylpyrrolidone is 30% by volume, the formulation further comprising propylene glycol.

17. A formulation according to claim 3 wherein the ivermectin is 10 mg/ml and the N-methylpyrrolidone is 30% by volume.

18. A formulation according to claim 17 comprising additionally 100 mg/ml Clorsulon.

19. A formulation according to claim 3 wherein ivermectin is 0.27% by weight, N-methylpyrrolidone is 40% by volume, the formulation further comprising 10% by volume water.

20. A formulation according to claim 3 wherein ivermectin is 10 mg/ml, N-methylpyrrolidone is 30% by volume, the formulation further comprising 1.5% by volume benzyl alcohol and 10% by volume water.

21. A formulation according to claim 3 wherein ivermectin is 10 mg/ml, N-methylpyrrolidone is 30% by volume, the formulation further comprising 20% by weight polyvinylpyrrolidone, 0.18% by weight methylparaben, and 0.02% by weight propylparaben.

22. A formulation according to claim 3 wherein ivermectin is 20 mg/ml, N-methylpyrrolidone is 40% by volume, the formulation further comprising 30% by weight polyethylene glycol.

23. A formulation according to claim 3 wherein ivermectin is 10 mg/ml, N-methylpyrrolidone is 30% by volume, the formulation further comprising 20% by weight polyvinylpyrrolidone and 1.5% by volume benzyl alcohol.

24. A formulation according to claim 3 wherein ivermectin is 10 mg/ml, N-methylpyrrolidone is 30% by volume, the formulation further comprising 10% by volume polysorbate 80, 10% by volume polyoxyethylene fatty acid ester and 1.5% by volume benzyl alcohol.

25. A formulation according to claim 3 wherein ivermectin is 5 mg/ml, N-methylpyrrolidone is 20% by volume, propylene glycol is 10% by volume, the formulation further comprising 0.01 mg/ml FD&C Blue #1 and water.

26. A formulation according to claim 5 wherein ivermectin is 5 mg/ml, N-methylpyrrolidone is 10% by volume, the formulation further comprising 0.01 mg/ml FD&C Blue #1, 1.5% by volume benzyl alcohol, and water.

27. A formulation according to claim 3 wherein ivermectin is 10 mg/ml, N-methylpyrrolidone is 5% by volume, propylene glycol is 20% by volume, the formulation further comprising polysorbate 80 10% by volume, benzyl alcohol 1.5% by volume, and water.

28. A formulation according to claim 3 wherein ivermectin is 10 mg/ml, N-methylpyrrolidone is 20% by volume, propylene glycol is 20% by volume, the formulation further comprising 1.5% by volume benzyl alcohol, and water.

Preparation for Administration

The formula of the present invention is diluted before administration to the animals, plants, insects, or ground surface to be treated as follows. In this example, the formula is prepared for administration of ivermectin in the drinking water of fowl for the treatment of parasites, but the person of ordinary skill in the art will realize that the formula may be diluted for the administration of many pharmacologically active compounds to any type of animal, plant, insect, or surface.

Example 1

The 2% ivermectin solution is diluted 20-fold to 0.1% in water. From the 0.1%, 3.4 ml is dissolved in 5 liters (QS) of water. The dose to be administered in order to obtain effective treatment of various parasites depends on the size of the fowl to be treated (i.e., their drinking capacity). A 4.5 kg turkey will typically drink 600-1000 ml of water every 24 hours. This corresponds to a dose of 100-150 μgm/kg/day. It is found that a dose of 200 mg ivermectin/kg body weight/day is effective to completely eliminate roundworms (*Ascaridia*) and cecal worms (*Heterakis*) in turkeys in three days. The effective dose to administer to any other type of animal to treat a particular type of parasite can be easily determined by simply varying the dosage until arriving at an effective dose.

A non-aqueous, stable formulation of ivermectin was prepared and diluted into the drinking water of market male turkeys as described above. The turkeys had an average weight of 4.5 kg and had a history of roundworm infestation (*Ascaridias*). The birds were treated at levels of 10, 50, 100, 200, 250, 500, 1200, and 1400 mg/kg of body weight/day. The water consumption by the turkeys was normal and the birds did not refuse drinking water due to

treatment at any leve[redacted]he formulation was effective at complet[redacted]liminating any visible signs of roundworm infestation at levels down to 200 mg/kg body weight/day in three days.

The person of ordinary skill will realize that the present invention finds applicability for the administration of many pharmacologically and biologically active compounds. For example, the present invention may be applied to pesticides, nutrients or other compounds (some of which are listed below) for administration in drinking water, or for topical administration to animals, plants, or ground or other surfaces. The present invention is therefore applicable to treating any of the wide variety of diseases which may be treated by administration of a formulation of the present invention.

Pesticides

Many types of pesticides may be employed in the present invention, including herbicides, fungicides, growth regulators, insecticides, and acaracides. The following is a partial list of those compounds that may be utilized according to the present invention. The list is provided as representative examples and is not intended to be comprehensive and the person of ordinary skill will understand that many other compounds may also be utilized according to the present invention.

Acaracides

Clofentezine, formetanate hydrochloride, formetanate hydrochloride, hexythiazox, dicofol, fenbutatin oxide, abamectin, and milbemycin.

Fungicides

Metalaxyl, oxadixyl, Azoxystrobin, bayleton, triadimefon baytan, triadimenol, benomyl, chlorothalonil, captan, carboxin, cymoxanil, difenoconazole, mancozeb, difenoconazole, etridiazole, hymexazol, imazalil, fludioxonil, thiabendazole, thiophanate methyl, propiconazole

Growth regulators

Phenoxy Acetic Acids

Phenoxy Propionic Acids

Mecoprop

Phenoxy Butyric Acids

Benzoic Acids, such as Dicamba

Other growth regulators

Fluoroxypyr

Picloram

Triclopyr

Copyralid

Insecticides

Permethrin, Esfenvalerate, Carbaryl, Chlorpyrifos, Dimethoate, Malathion, Abamectin, Acephate, Diflubenzuron, Endosulfan, Oxydemeton methyl, Oxamyl, Methidathion, Imidacloprid, Cyromazine, Isazofos, Bendiocarb, Cyfluthrin, Diazinon, Bifenthrin, Carbofuran, Phosmet, Methoxychlor, Pirimicarb, Tebufenozide, Azadirachtin, Tefluthrin,

Herbicides

Photosynthesis inhibitors

Triazines and s-Triazines such as

Hexazinone

Metribuzin

Atrazine

Simazine

Cyanazine Prometon

Ametryn

Pigment Inhibitors, such as

Amitrole

Clomazone

Fluridone

Norflurazone

Substituted Ureas, such as

Diuron

Linuron

Tebuthiuron

Uracils, such as Bromacil

Terbacil

Other photosynthesis inhibitors, such as

Bentazon

Desmedipham

Methazole

Phenmedipham

Propanil

Pyridate

Mitotic disruptors:

Dinitroanilines, such as Oryzalin

Pendimethalin

Prodiamine

Trifluralin

Inhibitors of amino acid synthesis, such as

Glyphosate

Sulfonylureas, such as

Bensulfuron

Chlorimuron

Chlorsulfuron

Metsulfuron

Nicosulfuron

Primisulfuron

Sulfometuron

Thifensulfuron

Trisulfuron

Tribenuron

Imidazolinone, such as Imazamethabenz

Imazapyr

Imazaquin

Imazethapyr

Inhibitors of lipid biosynthesis, such as

Clethodim

Diclofop-methyl

Fenoxaprop-ethyl

Fluazifop-P-butyl

Haloxyfop-methyl

Quizalofop

Sethoxydim

Cell wall inhibitors, such as

Dichlobenil

Isoxaben

Cell membrane disruptors:

Bipyridylium compounds, such as:

Diquat

Paraquat

Diphenylethers, such

Acifluorfen

Fomesafen

Lactofen

Oxyfluorfen

Other herbicides

Glufosinate

Bromoxynil

Natural Insect Growth Regulators

Azadirachtin

Dihydroazadirachtin

Attractants

Plant Volatiles

Oil of Anise

Indole

Oil of Orange

Cinamaldehyde

Geraniol

Eugenol

Oil of Citronella

Repellants

Anthraquinone

Capsaicin

Linalool

Methyl Anthranilite

Cedarwood Oil

Miscellaneous Biochemicals

Canola Oil

Neem Oil

Castor Oil

Jojoba Oil

We claim:

1. A non-aqueous composition comprising:

an emulsifier;

a polyol;

benzyl alcohol; and

a pharmacologically or biologically active compound.

2. The composition of claim 1 provided in a form suitable for dilution in aqueous solutions.

3. The composition of claim 1 wherein the pharmacologically active compound is a parasiticide.

4. The composition of claim 3 wherein the parasiticide is selected from the group consisting of: ivermectin, doramectin, avermectin, abamectin, milbemycin, amprolium, bacitracin, chlortetracycline, erythromycin, lincomycin/spectinomycin, neomycin, oxytetracycline, piperazine, sarafloxacin, spectinomycin, sulfachloro-pyrazine, sulfadimethoxine, sulfamethazine, sulfaquinoxaline, tetracycline, and tylosin.

5. The composition of claim 4 wherein the parasiticide is selected from the group consisting of: bacitracin, chlortetracycline, erythromycin, lincomycin, oxytetracycline, piperazine, spectinomycin, and tetracycline.

6. The composition of claim 3 wherein the parasiticide is ivermectin.

7. The composition of claim 1 wherein the emulsifier is selected from the group consisting of: polysorbate 80, polysorbate 85, polysorbate 20, and polysiloxanes [organosilicones].

8. The composition of claim 7 wherein the emulsifier is polysorbate 80.

9. The composition of claim 1 wherein the polyol is propylene glycol.

10. The composi[redacted]of claim 1 wherein the emulsifier is poly[redacted]ate 80 and the polyol is propylene glycol.

11. The composition of claim 10 wherein the pharmacologically active compound is ivermectin.

12. A non-aqueous composition comprising:

an emulsifier;

n-methyl pyrrolidone;

benzyl alcohol; and

a pharmacologically or biologically active compound.

13. The composition of claim 12 provided in a form suitable for dilution in aqueous solutions and wherein the pharmacologically active compound is a parasiticide.

14. The composition of claim 15 wherein the parasiticide is selected from the group consisting of: bacitracin, chlortetracycline, erythromycin, lincomycin, oxytetracycline, piperazine, spectinomycin, and tetracycline.

15. The composition of claim 13 wherein the parasiticide is ivermectin.

16. The composition of claim 18 wherein the emulsifier is polysorbate 80 and the pharmacologically active compound is ivermectin.

17. A method of administering a pharmacologically active compound to a vertebrate, comprising:

providing the pharmacologically active compound in the form of a non-aqueous formulation which further comprises

an emulsifier,

benzyl alcohol, and

a poly

diluting the formulation in an aqueous solution; and

administering the compound in the drinking water of the vertebrate.

18. The method of claim 17 wherein the pharmacologically active compound is water labile or water-insoluble.

19. The method of claim 17 wherein the vertebrate is a fowl.

20. The method of claim 17 wherein the vertebrate is a mammal.

21. The method of claim 20 wherein the mammal is selected from the group consisting of: bovines, equines, ovines, caprines, canines, felines, and porcines.

22. The method of claim 17 wherein the pharmacologically active compound is a parasiticide.

23. The method of claim 22 wherein the parasiticide is ivermectin.

24. The method of claim 17 wherein the pharmacologically active compound is selected from the group consisting of: ivermectin, doramectin, avermectin, abamectin, milbemycin, amprolium, bacitracin, chlortetracycline, erythromycin, lincomycin/spectinomycin, neomycin, oxytetracycline, piperazine, sarafloxacin, spectinomycin, sulfachloro-pyrazine, sulfadimethoxine, sulfamethazine, sulfaquinoxaline, tetracycline, and tylosin.

25. The composition of claim 24 wherein the parasiticide is selected from the group consisting of: bacitracin, chlortetracycline, erythromycin, lincomycin, oxytetracycline, piperazine, spectinomycin, and tetracycline.

26. A method of administering a pharmacologically active compound to a vertebrate, comprising:

providing the pharmacologically active compound in the form of a non-aqueous formulation comprising

an emulsifier,

benzyl alcohol,

n-methyl pyrrolidone;

diluting the formulation in an aqueous solution; and

administering the compound in the drinking water of the vertebrate.

27. The method of claim 26 wherein the pharmacologically active compound is water labile or water-insoluble.

28. The method of claim 26 wherein the vertebrate is a fowl or a mammal.

29. The method of claim 26 wherein the pharmacologically active compound is a parasiticide.

30. The method of claim 29 wherein the parasiticide is ivermectin.

31. The method of claim 26 wherein the pharmacologically active compound is selected from the group consisting of: ivermectin, doramectin, avermectin, abamectin, milbemycin, amprolium, bacitracin, chlortetracycline, erythromycin, lincomycin/spectinomycin, neomycin, oxytetracycline, piperazine, sarafloxacin, spectinomycin, sulfachloro-pyrazine, sulfadimethoxine, sulfamethazine, sulfaquinoxaline, tetracycline, and tylosin.

32. A method of administering a pharmacologically or biologically active compound to an organism comprising:

providing the biologically active compound in the form of a non-aqueous formulation further comprising an emulsifier, a polyol, and benzyl alcohol;

diluting the non-aqueous formulation in an aqueous solution;

topically apply the diluted formulation to the organism to be treated.

33. The method of claim 32 wherein the organism is a plant.

34. The method of claim 33 wherein the plant is an agricultural crop.

35. The method of claim 33 wherein the biologically active compound is a pesticide.

36. The method of claim 35 wherein the pesticide is selected from the group consisting of: clofentezine, formetanate hydrochloride, formetanate hydrochloride, hexythiazox, dicofol, fenbutatin oxide, abamectin, and milbemycin, metalaxyl, oxadixyl, azoxystrobin, bayleton, triadimefon baytan, triadimenol, benomyl, chlorothalonil, captan, carboxin, cymoxanil, difenoconazole, mancozeb, difenoconazole, etridiazole, hymexazol, imazalil, fludioxonil, thiabendazole, thiophanate methyl, propiconazole, phenoxy acetic acids, phenoxy propionic acids, mecoprop, phenoxy butyric acids, benzoic acids, fluoroxypyr, picloram, triclopyr, copyralid, permethrin, esfenvalerate, carbaryl, chlorpyrifos, dimethoate, malathion, abamectin, acephate, diflubenzuron, endosulfan, oxydemeton methyl, oxamyl, methidathion, imidácloprid, cyromazine, isazofos, bendiocarb, cyfluthrin, diazinon, bifenthrin, carbofuran, phosmet, methoxychlor, pirimicarb, tebufenozide, azadirachtin, tefluthrin, hexazinone, metribuzin, atrazine, simazine, cyanazine prometon, ametryn, amitrole, clomazone, fluridone, norflurazone, diuron, linuron, tebuthiuron, bromacil, terbacil bentazon, desmedipham, methazole, phenmedipham, propanil, pyridate, oryzalin, pendimethalin, prodiamine, trifluralin, glyphosate, bensulfuron, chlorimuron, chlorsulfuron, metsulfuron, nicosulfuron, primisulfuron, sulfometuron, thifensulfuron, trisulfuron, tribenuron, imazamethabenz, imazapyr, imazaquin, imazethapyr, clethodim, diclofop-methyl, fenoxaprop-ethyl, fluazifop-P-butyl, haloxyfop-methyl, quizalofop, sethoxydim, dichlobenil, isoxaben, diquat, paraquat, acifluorfen, fomesafen, lactofen, oxyfluorfen, glufosinate, bromoxynil, azadirachtin, dihydroazadirachtin, attractants, plant volatiles, oil of anise, indole, oil of orange, cinamaldehyde, geraniol, eugenol, oil of citronella, anthraquinone, capsaicin, linalool, methyl anthranilite, cedarwood oil, canola oil, neem oil, castor oil, jojoba oil, doramectin, gibberellic acid, oil of eucalyptus, linalool.

37. The method of claim 36 wherein the pesticide is abamectin, ivermectin, spinosad, milbemycin oxime, milbemectin, doramectin, permethrin, bifenthrin, azadirachtin, glyphosate, nicosulfuron, bromoxynil, indole, butyric acid, gibberellic acid, capsaicin, methyl anthranilite, neem oil, eugenol, oil of citronella, oil of eucalyptus, linalool.

38. The method of claim 32 wherein the pharmacologically active compound is topically applied by spraying onto the organism to be treated.

39. A method of administering a pharmacologically or biologically active compound to an organism comprising:

providing the biologically active compound in the form of a non-aqueous formulation further comprising an emulsifier, n-methyl pyrrolidone, and benzyl alcohol;

diluting the non-aqueous formulation in an aqueous solution;

topically applying the diluted formulation to the organism to be treated.

40. The method of claim 39 wherein the organism is an agricultural crop.

41. The method of claim 39 wherein the biologically active compound is a pesticide.

42. The method of claim 41 wherein the pesticide is selected from the group consisting of: clofentezine, formetanate hydrochloride, formetanate hydrochloride, hexythiazox, dicofol, fenbutatin oxide, abamectin, and milbemycin, metalaxyl, oxadixyl, azoxystrobin, bayleton, triadimefon baytan, triadimenol, benomyl, chlorothalonil, captan, carboxin, cymoxanil, difenoconazole, mancozeb, difenoconazole, etridiazole, hymexazol, imazalil, fludioxonil, thiabendazole, thiophanate methyl, propiconazole, phenoxy acetic acids, phenoxy propionic acids, mecoprop, phenoxy butyric acids, benzoic acids, fluoroxypyr, picloram, triclopyr, copyralid, permethrin, esfenvalerate, carbaryl, chlorpyrifos, dimethoate, malathion, abamectin, acephate, diflubenzuron, endosulfan, oxydemeton methyl, oxamyl, methidathion, imidacloprid, cyromazine, isazofos, bendiocarb, cyfluthrin, diazinon, bifenthrin, carbofuran, phosmet, methoxychlor, pirimicarb, tebufenozide, azadirachtin, tefluthrin, hexazinone, metribuzin, atrazine, simazine,

cyanazine pro[redacted]n, ametryn, amitrole, clomazone, flurido[redacted]norflurazone, diuron, linuron, tebuthiuron, bromacil, terbacil bentazon, desmedipham, methazole, phenmedipham, propanil, pyridate, oryzalin, pendimethalin, prodiamine, trifluralin, glyphosate, bensulfuron, chlorimuron, chlorsulfuron, metsulfuron, nicosulfuron, primisulfuron, sulfometuron, thifensulfuron, trisulfuron, tribenuron, imazamethabenz, imazapyr, imazaquin, imazethapyr, clethodim, diclofop-methyl, fenoxaprop-ethyl, fluazifop-P-butyl, haloxyfop-methyl, quizalofop, sethoxydim, dichlobenil, isoxaben, diquat, paraquat, acifluorfen, fomesafen, lactofen, oxyfluorfen, glufosinate, bromoxynil, azadirachtin, dihydroazadirachtin, attractants, plant volatiles, oil of anise, indole, oil of orange, cinamaldehyde, geraniol, eugenol, oil of citronella, anthraquinone, capsaicin, linalool, methyl anthranilite, cedarwood oil, canola oil, neem oil, castor oil, jojoba oil, doramectin, gibberellic acid, oil of eucalyptus, linalool.

43. A method of administering a pharmacologically or biologically active compound to a surface comprising:

providing the pharmacologically or biologically active compound in the form of a non-aqueous formulation comprising an emulsifier, a polyol or n-methyl pyrrolidone, and benzyl alcohol;

diluting the non-aqueous formulation in an aqueous solution;

topically applying the diluted formulation to the surface to be treated.

44. The method of claim 43 wherein the surface is a ground surface.

45. A non-aqueous composition comprising:

an emulsifier;

a polyol;

a monohydric alcohol; and

a pharmacologically or biologically active compound.

46. The compositi[redacted]f claim 45 provided in a form suitable fo[redacted]ution in aqueous solutions.

47. The composition of claim 45 wherein the pharmacologically active compound is a parasiticide.

48. The composition of claim 47 wherein the parasiticide is selected from the group consisting of: ivermectin, doramectin, avermectin, abamectin, milbemycin, amprolium, bacitracin, chlortetracycline, erythromycin, lincomycin/spectinomycin, neomycin, oxytetracycline, piperazine, sarafloxacin, spectinomycin, sulfachloro-pyrazine, sulfadimethoxine, sulfamethazine, sulfaquinoxaline, tetracycline, and tylosin.

49. The composition of claim 48 wherein the parasiticide is selected from the group consisting of: bacitracin, chlortetracycline, erythromycin, lincomycin, oxytetracycline, piperazine, spectinomycin, and tetracycline.

50. The composition of claim 47 wherein the parasiticide is ivermectin.

51. The composition of claim 45 wherein the emulsifier is polysorbate 80 and the polyol is propylene glycol.